

## PCT



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A 3054	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 03/03928	International filing date (day/month/year) 15.04.2003	Priority date (day/month/year) 19.04.2002
International Patent Classification (IPC) or both national classification and IPC A61K39/395, A61K39/395		
Applicant AFFIRMED THERAPEUTICS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.  
  
☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
  
 These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:
  - I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

Date of submission of the demand  14.11.2003	Date of completion of this report  01.06.2004
Name and mailing address of the international preliminary examining authority:   European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer  Nooij, F  Telephone No. +31 70 340-3267 

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/03928

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

### Description, Pages

1-30 as originally filed

### Claims, Numbers

1-27 as originally filed

### Drawings, Sheets

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes: Claims	15,27
	No: Claims	1-14,16-26
Inventive step (IS)	Yes: Claims	
	No: Claims	1-27
Industrial applicability (IA)	Yes: Claims	1-27
	No: Claims	

**2. Citations and explanations**

**see separate sheet**

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The following documents are referred to in this communication:

*D1*: S. KIPRIYANOV ET AL.: 'Novel recombinant bispecific molecules for immunotherapy of blood malignancies.' INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE, vol. 8, no. suppl. 1, 2001, page S24, XP008013589.

*D2*: T. KUDO ET AL.: 'Specific targeting immunotherapy of cancer with bispecific antibodies.' TOHOKU JOURNAL OF EXPERIMENTAL MEDICINE, vol. 188, no. 4, August 1999 (1999-08), pages 275-288, XP002932520, Sendai, Japan.

*D3*: C. RENNER ET AL.: 'Cure of xenografted human tumors by bispecific monoclonal antibodies and human T cells.' SCIENCE, vol. 264, 6 May 1994 (1994-05-06), pages 833-835, XP001093779, Washington, DC, USA.

2. The term 'features (b) and (d) or (b) and (c)', especially the word 'or', used in present claim 1 is vague and indefinite and as such renders the scope of the claim unclear. The following combinations of b, c, and d could be interpreted:

- combination 1: (b x d) and (b x c)
- combination 2: (b x d) and (b x d)
- combination 3: (b x c) and (b x c)
- combination 4: (b x b x c) and (b x d x c)

3. However, from the examples of the underlying application, esp. example 5, it seems that only combination 1 is supported and disclosed, and makes a contribution to the art. A discussion with regard to novelty and inventive step will therefore be restricted to claimed subject-matter as represented by said combination 1.

4. *D1* discloses a panel of bispecific diabodies with the dual specificity to human CD19 or CD30 on non-Hodgkin's or Hodgkin's lymphoma cells, respectively, and either to CD3, or CD28 or CD16 on human T cells or NK effector cells. It is widely known in the art that CD3 and CD28 are expressed on T cells, that CD16 is expressed on NK cells, i.e. CD3-epsilon negative cells, and that T cells and NK cells represent two different populations of effector cells. T cells and NK cells are

the only effector cells mentioned in this document. A combination of bispecific diabodies retargeting different populations of human effector cells towards the tumor was resorted to significantly enhance the therapeutic effect. From this it is clear that a bispecific diabody with one specificity for a tumor antigen and the other for a T cell is combined with a bispecific diabody with one specificity for a tumor antigen and the other for an NK cell.

5. *D2* discloses tumor therapy with bispecific antibodies and combinations thereof, e.g. with the following specificities: (CD3 x Muc1) and (CD28 x Muc1) and (CD2 x Muc1). It is widely known that CD3 and CD28 are expressed on T cells, while CD2 is expressed on T cells and on NK cells, i.e. the latter being CD3-epsilon negative cells. The allegation by the applicant that *D2* discloses the use of only T-LAK cells as effector cells seems unjustified: On page 280, line 3, it is disclosed that the above-mentioned combination of 3 different bispecific antibodies is tested by using peripheral blood mononuclear cells, which are known to include both T cells and NK cells.
6. For the reasons given under points 4 and 5, the subject-matter of present claims **1-14** and **16-26** is not new in the sense of Article 33(3) PCT.
7. With regard to present claim **27**, *D1* and *D2* are equally considered to represent the most relevant state of the art and disclose combinations of (recombinantly-produced) bispecific antibodies for therapeutic use.  
The subject-matter of said claim differs in that the use of polynucleotides (and vectors comprising them) encoding said bispecific antibodies for gene therapy is claimed.  
The problem to be solved by the present invention may therefore be regarded as providing alternative therapeutic ways to represent a combination of said bispecific antibodies to the host's immune system.  
The proposed solution is the use of polynucleotides (and vectors comprising them) encoding the bispecific antibodies that make up the therapeutic combinations.  
This solution cannot, however, be considered as involving an inventive step for the following reasons: *D3* discloses a recombinantly produced bispecific antibody, and vectors comprising the nucleotides encoding said bispecific antibody. It also discloses the therapeutic use of the bispecific antibody, as well as the therapeutic use of a gene construct, e.g. a vector comprising the polynucleotides encoding said bispecific antibody, for gene therapy.  
It is therefore obvious for a skilled person to choose gene therapy as a way to

present bispecific constructs, or combinations thereof, to the host's immune system.

8. Present dependent claim **15** does not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step for the following reasons:

The feature of the linking of an effector molecule for detection or therapy is a matter of normal design procedure, see e.g. *D2*, page 285, lines 18-22, in which mutated superantigen SEA-D227A has been conjugated to bispecific antibody (anti-Muc1 x anti-CD28). The inclusion of said feature in any of the antibodies of the claimed combination would therefore be an obvious design possibility for the skilled person.

9. In view of points 7 and 8, the subject-matter of present claims **15** and **27** does not involve an inventive step in the sense of Article 33(3) PCT.